Remarks

Applicants have amended claims 1, 3 & 9. Applicants respectfully submit that no new prohibited matter has been introduced by this Preliminary Amendment. While written description support for the claims can be found throughout the specification, specific support for claims can be found on page 25, line 18 to page 26, line 9 and in Figure 6.

Summary of Final Office Action

1. Claims 1-7 were rejected under 35 U.S.C. 102(a) as being anticipated by Nagene *et al.* (1998) Proc. AACR Spec. Conf.

2. Claims 1-16 were rejected under 35 U.S.C. 103 based upon Han *et al.* (1996) Cancer Res. 56, 3859-3861 in view of Reed *et al.* (U.S. Patent 5,831,066) in further view of Tsai *et al.* (1996) Cancer Res. 56, 937-1177.

Rejection under 35 U.S.C. 102(a)

Claims 1-7 were rejected under 35 U.S.C. 102(a) as being anticipated by Nagene *et al.* Applicants' agent is in the process of obtaining an affidavit from the inventors establishing that the cited reference discloses Applicants' own work. Applicants will submit this affidavit in a supplemental amendment as soon as it is available. In the interim, Applicants respectfully request that this rejection be held in abeyance with the understanding that the aforementioned affidavit will be submitted as soon as it is available.

Rejection under 35 U.S.C. 103

Claims 1-16 were rejected under 35 U.S.C. 103 based upon Han *et al.* (1996) in view of Reed *et al.* in further view of Tsai *et al.* Applicants respectfully submit that there would be no motivation to combine the cited references.

The Office Action indicates that the underlying mechanism of Applicants' invention was appreciated by Tsai *et al.* (see Office Action at page 6, lines 21-23). The Office Action also indicates that the experimental results in the specification are not unexpected because Tsai *et al.* purportedly makes it clear that what would have been expected was an enhancement of the susceptibility of the cells to apoptosis (see Final Office Action at page 7, lines 2-6). Applicants bring to the Examiner's attention that

Tsai *et al.* do not disclose nor suggest resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene.

Applicants also note that the Han *et al.* reference does not even discuss apoptosis associated with a mutant EGFR. In light of these facts, Applicants respectfully submit that there would be no motivation to combine the cited references. To remedy these lack of teachings in the cited references, it appears that the Office Action is relying on the teachings of the specification. For instance, the Office Action asserts that an ordinary skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of a mutant EGFR (see Office Action at page 5, lines 12-18). Respectfully, neither reference discloses that a mutant EGFR is even involved in the modulation of the apoptosis in a tumor cell. This discovery can be found only in the instant application and therefore, reliance on this motivation to combine the references is improper.

Applicants have previously argued that the unexpected, synergistic results disclosed in the experimental data in the specification are indicative of non-obviousness (see Applicants' Amendment dated December 6, 2001 at pages 6-8) and the Office Action acknowledged that the results are not merely additive (see Office Action at page 7, lines 1-2). The Office Action also indicated that the amounts taught or suggested by the references are those which would meet the claim limitations (see Office Action at page 6, lines 18-20). Applicants have amended claims 1, 3 & 9 to provide the feature that the kinase inhibitor be present in a synergistically effective amount. Applicants respectfully submit that the cited references, neither alone nor in combination, suggest an amount of a tyrosine kinase inhibitor synergistically effective to reduce resistance to induction of apoptosis or resistance to an increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR, and therefore do not teach all the limitations of the claimed invention.

In view of the foregoing discussion, Applicants respectfully submit that the Office Action has not adduced a legally sufficient prima facie case of obviousness. Accordingly, reversal of the rejection would be appropriate.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned Version with markings to show changes made.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit

any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted
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Dated: **November 14, 2002**
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Four times amended) A method of modulating an apoptosis-inhibiting effect in a target cell or tissue of a mutant EGFR gene, comprising administering to the cell or tissue an amount of a tyrosine kinase inhibitor that is synergistically effective to reduce resistance to induction of apoptosis or resistance to an increased rate of apoptosis in the target cell or tissue in combination with a therapy that is effective to induce apoptosis or to increase the rate of apoptosis in the cell or tissue.

9. (Thrice amended) A pharmaceutical composition comprising a mixture of:

(A) an amount of an agent that is effective to induce apoptosis or to increase a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is synergistically effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR.

13. (Thrice Amended) A kit for treating cancer comprising:

(A) an amount of an agent that is effective to induce apoptosis or increase a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is synergistically effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR.